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of Breast Cancer

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Severe Caloric Restriction during Adolescence and Incidence of Breast Cancer

INTRODUCTION

Conventional approaches in breast cancer prevention research have focused on women's adult life stages. The study of reproductive risk factors (except for age at menarche) and the influence of dietary modifications have targeted periods, which may be beyond the most vulnerable phases of the mammary gland. To target preventive efforts it is crucial to identify the time period during a women's life during which her mammary tissue is susceptible to lifestyle influences. If the animal model applies to the human mammary gland, breast tissue will be most susceptible to carcinogens during adolescence. To confirm this hypothesis, important events during adolescence that might affect the mammary gland have to be identified. Few influences with great between-person-variation that occur during adolescence can be measured. One dramatic experience with increasing incidence among girls in Western Societies is anorexia nervosa. This severe restriction of caloric intake during a prolonged period during or right after puberty is of particular interest since caloric restriction has reduced breast cancer incidence in the animal model. Despite the obvious relevance of this question, it has not been studied previously as data on anorexia during adolescence and breast cancer outcomes from the same women are difficult to obtain.

BODY

Research Accomplishments

We conducted a retrospective cohort study in Sweden. A cohort of exposed women, i.e. women who had been hospitalized for anorexia nervosa between 1965 and 1998 was retrospectively formed and followed for the occurrence of breast cancer by linkage with the Swedish Cancer Registry, the Swedish Death Registry, and the Emigration Registry using the National Registration Number (NRN), a unique identifier for each resident of Sweden. We ascertained cancers diagnosed after 1965, the date and cause of death after 1965, and date of censoring due to emigration. The observed cancer numbers were compared to the expected cancer incidence rates based on rates in the female Swedish population in 5-year age intervals during the same calendar time period.

Study Population and Ascertainment of Exposure

Using the Swedish Inpatient Registry, we identified all women in Sweden who were hospitalized and treated for severe anorexia nervosa between 1965 and 1998. The Swedish Inpatient Registry was initiated in 1965 and is comprised of hospital-provided somatic and psychiatric medical services in the Swedish population. Each record contains the medical procedure, discharge diagnoses coded according to the International Classification of Diseases (ICD-7: 1965-1968; ICD-8: 1969-1987; ICD-9: 1988-onwards), and the NRN. The Register is complete within Swedish counties and covered 60% of the Swedish population in 1969, 75% in 1978, 85% in 1983, and the entire Swedish population since 1987.

Anorexia nervosa is defined in this study as having received inpatient care for the disease. A hospitalization for anorexia nervosa was identified by discharge diagnoses ICD-7 codes 316.99 and 784.09, ICD-8 code 306.50, and ICD-9 code 307B. This study was restricted to a first hospitalization for anorexia nervosa.

We identified 7656 women from the Swedish Inpatient Registry who were hospitalized for anorexia nervosa between 1965 and 1998, of whom 7303 women were hospitalized for anorexia nervosa prior to age 40. This anorexia population excluded 31 women who were diagnosed with cancer prior to their first discharge from hospitalization for anorexia nervosa.

Ascertainment of Outcomes

All first primary incident cancers diagnosed among our anorexia cohort were ascertained through record linkage with the Swedish Cancer Registry. The Swedish Cancer Registry contains all diagnoses of incident cancer among Swedish residents from January 1, 1958, to December 31, 2000 and its completeness has been evaluated to exceed 95%. The reports list the NRN and the cancer diagnosis according to the ICD-7 codes.

Assessment of Effect Modifiers

The Swedish Fertility Registry has information on every birth given in Sweden for all women born in 1925 and thereafter. We obtained information on parity status from this register for the members of our anorexia cohort.

Statistical Analysis

Person-time of follow-up was calculated for each member of the anorexia cohort from the date of first discharge from hospitalization for anorexia nervosa until the diagnosis of cancer, death, emigration, or December 31, 2000 (end of follow-up), whichever occurred first. The expected number of cancer cases in our cohort was calculated by multiplying the 5-year-age-interval- and calendar year-specific cancer rates of the general Swedish population by the person-time accumulated in each interval of the exposed population after censoring for death, emigration, or end of follow-up.

A standardized incidence ratio (SIR) was calculated as the ratio of the observed number of first primary cancer cases to that expected. A 95% confidence interval around the SIR was constructed based on the assumption that the observed number follows a Poisson distribution.

Effect modification by parity status was assessed by dividing the cohort into nulliparous and parous women based on the parity information obtained from the Fertility Registry. Parous women contributed person-time as nulliparae until they gave birth.

Results

The distribution of women hospitalized for anorexia nervosa in our cohort by age and calendar year of discharge diagnosis is presented in Table 1. The majority of anorexia cases (73%) were diagnosed prior to age 20.

Table 1: Distribution of women hospitalized for anorexia nervosa in Sweden between 1965 and 1998 by age at discharge and calendar year of discharge

Calendar year of discharge	Age at discharge of hospitalization for anorexia nervosa		
	0-19	20-29	30-39
1965-1974	278	184	49
1975-1984	2554	451	172
1985-1994	2146	742	180
1995-1998	353	152	42
Total	5331	1529	443

Among the 7303 women who were diagnosed with anorexia prior to age 40, we identified 52 women who were diagnosed with any type of cancer during 96,887 person-years of follow-up between 1965 and 2000; the expected number of cancer cases was 56.6. The standardized incidence ratio (SIR) for all types of cancers combined was 0.92 (95% CI 0.69-1.21) [Table 2].

Table 2: Standardized incidence ratios (SIRs) for cancer among 7303 Swedish women with a hospital discharge diagnoses of anorexia nervosa between 1965 and 1998.

Cancer	Observed Number of Cases	Expected Number of Cases ¹	SIR ² (95% CI ³)
All Cancers	52	56.6	0.92 (0.69-1.21)
Breast Cancer	7	14.8	0.47 (0.19-0.97)

¹ Based on the general Swedish female population

² SIR = Standardized Incidence Ratio

³ 95% CI = 95% confidence interval

Among women who were diagnosed with anorexia prior to age 40, the SIR for breast cancer was 0.47 (95% CI 0.19-0.97) [Table 2]. Seven women in this group developed breast cancer. The expected number of breast cancer cases was 14.8. Among women diagnosed with anorexia nervosa prior to age 20, no case of breast cancer occurred; the number of breast cancer expected in this group was 2.7. Among women diagnosed between age 20 and 29, four cases were diagnosed and 6.4 expected, and among women diagnosed with anorexia between age 30 and 39, three cases were observed and 5.7 expected.

In our anorexia cohort, 73% of women remained nulliparous throughout the observation period. Among women who remained nulliparous, the SIR for breast cancer was 0.77 (95% CI 0.25-1.79) during 78,984 person-years of follow-up. The corresponding value among parous women was 0.24 (95% CI 0.03-0.87) (Table 3).

Table 3: Standardized incidence ratios (SIRs) for cancer among 1942 parous and 5361 nulliparous Swedish women with a hospital discharge diagnoses of anorexia nervosa between 1965 and 1998 by parity status.

Cancer	Observed Number of Cases	Expected Number of Cases ¹	SIR ² (95% CI ³)
All			
Parous	16	24	0.67 (0.38-1.08)
Nulliparous	32	30	1.05 (0.72-1.48)
Breast			
Parous	2	8.3	0.24 (0.03-0.87)
Nulliparous	5	6.5	0.77 (0.25-1.79)

¹ Based on the general Swedish female population

² SIR = Standardized Incidence Ratio

³ 95% CI = 95% confidence interval

KEY RESEARCH ACCOMPLISHMENTS

- Severe caloric restriction during early life reduces incidence of breast cancer
- Women with anorexia nervosa had a 53% lower risk of breast cancer later in life
- This risk reduction was strongest among parous women; parous women with anorexia had a 76% lower risk of breast cancer

REPORTABLE OUTCOMES

- Publication in the Journal of the American Medical Association
Michels KM, Ekbom A. Caloric restriction and incidence of breast cancer. JAMA 2004;291:1226-30.

CONCLUSIONS

Our current findings indicate, that diet during early life may have an important effect on mammary tissue and that the animal model indicating a reduction in cancer risk associated with a low caloric intake may apply to humans. The effect seems particularly strong among parous women, resembling the environment of developing countries where women experience caloric restriction but go on to become pregnant and deliver children. Breast cancer rates in developing countries are considerably lower than in most affluent countries.

Bibliography of All Publications

Michels KB, Ekbom A. Caloric restriction and incidence of breast cancer. *JAMA* 2004;291:1226-30

ORIGINAL CONTRIBUTION

Caloric Restriction and Incidence of Breast Cancer

Karin B. Michels, ScD, MSc, MPH

Anders Ekbom, MD, PhD

RESTRICTING CALORIC INTAKE is one of the most effective ways to extend lifespan and to reduce spontaneous tumor occurrence in experimental animals.^{1,2} Caloric restriction has an important protective role in experimental mammary carcinogenesis.^{3,4} A recent meta-analysis summarized the available evidence of the effect of energy restriction on spontaneous mammary tumors in mice.⁵ The combined estimate for the 14 included studies implied that the energy-restricted animals developed 55% (95% confidence interval [CI], 41%-69%) fewer mammary tumors than did those in the control groups, irrespective of the type of restricted nutrient.⁵ The authors called for dietary cohort studies to gain insight into the effects of energy restriction on development of breast cancer in humans.⁵

Reduced caloric intake in experimental animals has been found to be accompanied by lower levels of circulating insulin, insulin-like growth factors I and II, and epidermal growth factor, as well as by modified cellular responsiveness to estrogens, enhanced immunologic responsiveness, alterations in cell cycle regulation, lower rates of cellular proliferation, increased DNA repair, reduced expression of oncogenes, and enhanced expression of tumor suppressor genes.⁵⁻¹⁰

Energy restriction may be crucial during early life and prior to first pregnancy, when mammary tissue is especially susceptible to carcinogenic processes.^{11,12} This hypothesis is supported

Context Restricting caloric intake is one of the most effective ways to extend lifespan and to reduce spontaneous tumor occurrence in experimental animals, but whether similar associations hold in humans has not been appropriately studied.

Objective To determine whether caloric restriction in early life reduces the risk of invasive breast cancer.

Design, Setting, and Participants Retrospective cohort study using data from the Swedish Inpatient Registry, the Swedish Cancer Registry, the Swedish Death Registry, and the Swedish Fertility Registry. Participants were 7303 Swedish women hospitalized for anorexia nervosa prior to age 40 years between 1965 and 1998. Women were excluded (n=31) if they were diagnosed with cancer prior to their first discharge from hospitalization for anorexia nervosa.

Main Outcome Measure Incidence of invasive breast cancer.

Results Compared with the Swedish general population, women hospitalized for anorexia nervosa prior to age 40 years had a 53% (95% confidence interval [CI], 3%-81%) lower incidence of breast cancer; nulliparous women with anorexia nervosa had a 23% (95% CI, 79% higher to 75% lower) lower incidence, and parous women with anorexia nervosa had a 76% (95% CI, 13%-97%) lower incidence.

Conclusions Severe caloric restriction in humans may confer protection from invasive breast cancer. Low caloric intake prior to first birth followed by a subsequent pregnancy appears to be associated with an even more pronounced reduction in risk.

JAMA. 2004;291:1226-1230

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by the observation that greater height, which although genetically influenced still reflects nutritional status and hence caloric intake during growth, is associated with an increased incidence of breast cancer.^{13,14}

Energy restriction is difficult to study in humans. One marker of caloric restriction is anorexia nervosa, an illness that occurs generally during adolescence or early adulthood and is characterized by very low caloric intake, low body mass index (BMI), and amenorrhea.

We conducted a retrospective cohort study in Sweden to evaluate whether women with anorexia nervosa severe enough to require hospitalization and treatment have a lower incidence of breast cancer than expected in the general population.

METHODS

Study Design

A cohort of Swedish women who had been hospitalized for anorexia nervosa between 1965 and 1998 was retrospectively formed and followed up for the occurrence of breast cancer by linkage with the Swedish Cancer Registry, the Swedish Death Registry, and the Emigration Registry using the National Registration Number, a unique

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identifier for each resident of Sweden. We ascertained cancers diagnosed after 1965, the date and cause of death after 1965, and date of censoring due to emigration. The observed cancer numbers were compared with the expected cancer incidence rates based on rates in the female Swedish population in 5-year age intervals during the same calendar period. The study was approved by the institutional review board of the Brigham and Women's Hospital, Boston, Mass, and by the Office for Human Research Protection at the Karolinska Institute, Stockholm, Sweden.

Study Population and Ascertainment of Exposure

Using the Swedish Inpatient Registry, we identified all women in Sweden who were hospitalized and treated for severe anorexia nervosa between 1965 and 1998. The Swedish Inpatient Registry was initiated in 1965 and is composed of hospital-provided somatic and psychiatric medical services in the Swedish population. Each record contains the medical procedure, discharge diagnoses coded according to the *International Classification of Diseases*, seventh through ninth revisions (ICD-7: 1965-1968; ICD-8: 1969-1987; ICD-9: 1988 forward), and the National Registration Number. The register is complete within Swedish counties and covered 60% of the Swedish population in 1969, 75% in 1978, 85% in 1983, and the entire Swedish population since 1987.

Anorexia nervosa is defined in this study as having received inpatient care for the disease. A hospitalization for anorexia nervosa was identified by discharge diagnoses ICD-7 codes 316.99 and 784.09, ICD-8 code 306.50, and ICD-9 code 307B. This study was restricted to a first hospitalization for anorexia nervosa.

We identified 7303 women from the Swedish Inpatient Registry who were hospitalized for anorexia nervosa prior to age 40 years between 1965 and 1998. This anorexia population excluded 31 women who were diagnosed with can-

Table 1. Distribution of Women Hospitalized for Anorexia Nervosa in Sweden Between 1965 and 1998, by Age at Discharge and Calendar Year of Discharge

Calendar Year of Discharge	Age at Discharge, y		
	0-19 (n = 5331)	20-29 (n = 1529)	30-39 (n = 443)
1965-1974	278	184	49
1975-1984	2554	451	172
1985-1994	2146	742	180
1995-1998	353	152	42

cer prior to their first discharge from hospitalization for anorexia nervosa.

Ascertainment of Outcomes

All first primary incident cancers diagnosed among our anorexia cohort were ascertained through record linkage with the Swedish Cancer Registry, which contains all diagnoses of incident cancer among Swedish residents from January 1, 1958, to December 31, 2000, and its completeness has been evaluated to exceed 95%.^{15,16} The reports list the National Registration Number and the cancer diagnosis according to the ICD-7 codes.

Assessment of Effect Modifiers

The Swedish Fertility Registry has information on every birth in Sweden among all women born in 1925 and thereafter. We obtained information on parity status from this registry for the members of our anorexia cohort.

Statistical Analysis

Person-time of follow-up was calculated for each member of the anorexia cohort from the date of first discharge from hospitalization for anorexia nervosa until the diagnosis of cancer, death, emigration, or December 31, 2000 (end of follow-up), whichever occurred first. The expected number of cancer cases in our cohort was calculated by multiplying the 5-year age interval- and calendar year-specific cancer rates of the general Swedish population by the person-time accumulated in each interval of the exposed population after censoring for death, emigration, or end of follow-up.

A standardized incidence ratio (SIR) was calculated as the ratio of the ob-

served number of first primary cancer cases to the number expected.¹⁷ A 95% CI around the SIR was constructed based on the assumption that the observed number follows a Poisson distribution.¹⁷

Effect modification by parity status was assessed by dividing the cohort into nulliparous and parous women based on the parity information obtained from the Swedish Fertility Registry. Parous women contributed person-time as nulliparae until they gave birth.

RESULTS

The distribution of women hospitalized for anorexia nervosa in our cohort by age and calendar year of discharge diagnosis is presented in TABLE 1. The majority of anorexia cases (73%) were diagnosed prior to age 20 years.

Among the 7303 women who were diagnosed with anorexia prior to age 40 years, we identified 52 women who were diagnosed with any type of cancer during 96887 person-years of follow-up between 1965 and 2000; the expected number of cancer cases was 56.6. The SIR for all types of cancers combined was 0.92 (95% CI, 0.69-1.21) (TABLE 2).

Among women who were diagnosed with anorexia prior to age 40 years, the SIR for breast cancer was 0.47 (95% CI, 0.19-0.97) (Table 2). Seven women in this group developed breast cancer. The expected number of breast cancer cases was 14.8; thus, women in this group had a 53% (95% CI, 3%-81%) lower incidence of breast cancer than the Swedish general population. Among women diagnosed with anorexia nervosa prior to age 20 years, no

Table 2. Standardized Incidence Ratios for Cancer Among Parous (n = 1942) and Nulliparous (n = 5361) Swedish Women With a Hospital Discharge Diagnosis of Anorexia Nervosa Between 1965 and 1998, Overall and by Parity Status

Type of Cancer	Observed No. of Cases	Expected No. of Cases*	SIR (95% CI)
Overall			
All cancers	52	56.6	0.92 (0.69-1.21)
Breast cancer	7	14.8	0.47 (0.19-0.97)
By Parity Status			
All cancers			
Parous	16	24.4	0.66 (0.38-1.07)
Nulliparous	36	32.2	1.12 (0.78-1.55)
Breast cancer			
Parous	2	8.3	0.24 (0.03-0.87)
Nulliparous	5	6.5	0.77 (0.25-1.79)

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.
 *Based on the general Swedish female population.

case of breast cancer occurred; the number of breast cancer cases expected in this group was 2.7. Among women diagnosed between the ages of 20 and 29 years, 4 cases were diagnosed and 6.4 expected; among women diagnosed with anorexia between the ages of 30 and 39 years, 3 cases were observed and 5.7 expected.

In our anorexia cohort, 73% of women remained nulliparous throughout the observation period. Among women who remained nulliparous, the SIR for breast cancer was 0.77 (95% CI, 0.25-1.79) during 78984 person-years of follow-up; there were 5 cases diagnosed and 6.5 expected, and thus women in this group had a 23% (95% CI, 79% increased to 75% decreased) reduced incidence of breast cancer. The corresponding SIR value among parous women was 0.24 (95% CI, 0.03-0.87) during 17903 person-years of follow-up; there were 2 cases diagnosed and 8.3 expected, and thus women in this group had a 76% (95% CI, 13%-97%) reduced incidence (Table 2).

Analyses of other hormone-dependent cancers such as uterine or ovarian cancer did not reveal a significant inverse association, but statistical power was limited (data not shown).

COMMENT

Among this Swedish cohort of women with a hospital discharge diagnosis of anorexia nervosa prior to age 40 years, we found a significant decrease in breast

cancer incidence compared with the general Swedish female population of comparable age and birth cohort. Because anorexia nervosa that requires hospitalization is associated with severe caloric restriction during a prolonged period of early life, we conclude that such starvation during adolescence and early adulthood may impact on mechanisms crucial for development of breast cancer. The majority of breast cancers in this cohort arose in premenopausal women due to the age structure of the cohort.

These findings confirm observations made in rodents in which caloric restriction has been a very effective measure to reduce cancer incidence. We are aware of only 1 other study in which the association between anorexia nervosa and cancer incidence was considered among humans. A study conducted in Denmark took a similar approach, linking the Danish Psychiatric Case Register and the National Registry of Patients to the Danish Cancer Registry.¹⁸ The authors report an SIR of 0.80 (95% CI, 0.52-1.18) for overall cancer incidence among 2151 women with a hospital discharge diagnosis of anorexia nervosa based on 25 observed cases. In this cohort, statistical power was limited to consider site-specific cancers. The SIR observed for breast cancer was 0.8 (95% CI, 0.3-1.7), but the study population was not restricted to women who experienced anorexia prior to age 40 years.¹⁸ In another study, prepubertal girls who

were exposed to the Norwegian famine in World War II and who consumed an average of 22% fewer calories had a lower subsequent rate of breast cancer than women from earlier or later birth cohorts.¹⁹

Among women with anorexia in our cohort who later had 1 or more children the risk of breast cancer was reduced by 76%. Among these women, we mimic the environment of developing countries where women experience caloric restriction but go on to become pregnant and deliver children. Rates of breast cancer in developing countries are considerably lower than in most affluent countries.²⁰ It is conceivable that caloric restriction during early periods of life is associated with decreased development of breast parenchyma and that subsequent differentiation of breast cells during pregnancy confers stronger protection than among women in industrialized countries. Hence, low rates of breast cancer in developing countries may be due to low caloric intake prior to first birth, and a particularly pronounced protection is conferred by subsequent pregnancy.

Among women with anorexia nervosa, later fertility does not seem to be compromised, but fecundability is reduced.^{21,22} In general, women with anorexia nervosa may have delayed childbirth and thus lower parity. In our cohort, only 26% of women gave birth after a diagnosis of anorexia nervosa, but due to the age structure of the cohort most women are still of childbearing age. In Sweden, the average age at first birth is currently 30 years.²³

A number of possible mechanisms may underlie our observations. Caloric restriction may have a direct effect on breast cell growth and development. Prolonged caloric restriction can also affect the expression of various oncogenes and tumor suppressor genes. Reduced levels of epidermal growth factor expression, reduced ERBB2 levels, a decrease in cyclin D1 expression, and increased p53 and p27 expression have been found in the mammary tissue of chronically calorie-restricted rodents.⁷⁻⁹

Furthermore, caloric restriction and anorexia have been found to reduce levels of estrogen (which may be manifested in amenorrhea)^{10,24} and insulin-like growth factor I (IGF-I).^{6,25} Recent research has identified IGF-I as an important biomarker for the prediction of breast cancer.^{26,27} IGF-I is a powerful growth hormone whose serum and tissue levels peak during adolescence.²⁸ Anorexia nervosa might lead to lower tissue levels of IGF-I during a crucial phase of mammary gland development and thus affect risk of breast cancer.

Anorexia nervosa is associated with amenorrhea and consequently a reduced number of lifetime ovulations, which might confer protection from breast cancer. Women with anorexia often enhance weight loss by strenuous physical activity. The epidemiologic data on the association between physical activity and risk of breast cancer are not conclusive, but more evidence supports an inverse relation with postmenopausal breast cancer^{29,30} than with premenopausal^{31,32} breast cancer. Some studies indicate a reduced risk of breast cancer among women who exercised heavily during their teenage years.^{33,34} Heavy exercise was associated with the strongest risk reduction in breast cancer among women with low BMI in at least 1 study.³⁵

Anorexia may be associated with considerable weight fluctuations, which have also been found to protect from breast cancer in the animal model.³⁶ We are aware of only 1 epidemiologic study that has considered weight cycling and breast cancer among humans.³⁷ In a population-based case-control study conducted in the United States, weight cycling was defined as losing 20 lb (9 kg) or more and gaining at least half of the lost weight back within 1 year; 1 cycle was sufficient to qualify an individual as a weight cyclist. No association was found with breast cancer.

The biological pathways of the association between body mass and the risk of breast cancer are complex, with opposing effects of a high BMI on premenopausal and postmenopausal risk of breast cancer.^{38,39} A number of re-

ports have related a high BMI during adolescence with a decreased risk of breast cancer.⁴⁰⁻⁴³ Coates and colleagues⁴⁴ have reported a U-shaped relation between relative weight in adolescence and later risk of breast cancer: women who were either much heavier or much thinner than average were at reduced risk. Both anorexia nervosa and obesity during adolescence may be associated with anovulation and thus a delayed onset of menarche. Alternatively, mechanisms underlying the protection conferred by low and high caloric intake may differ; while very low circulating levels of estrogen and other growth hormones might be protective, fairly high levels might induce early differentiation of breast cells.⁴⁵

Our study has a number of limitations. The number of cases observed in our cohort is limited. Furthermore, there is the possibility of unmeasured confounding. It is unlikely, however, that established risk factors for breast cancer, such as family history, would be related to anorexia nervosa. While our cohort of women with anorexia may differ from the general population in some aspects other than total caloric intake, women with anorexia who go on to become pregnant are more similar to the general population, which lends support to our conclusions. Reproductive factors (eg, age at menarche, parity, age at first birth) and anthropometric variables (eg, height, BMI) might be in the causal pathway of the association of interest; thus, we would not want to adjust for them. Furthermore, lower parity and a later age at first birth would place women with anorexia at a higher risk of breast cancer. In this Swedish cohort, exposure and outcome were ascertained with high accuracy. Neither differential nor nondifferential misclassification of exposure or disease are probable. Therefore, it is unlikely that our results are due to bias.

Our observations suggest an important role for caloric intake in the etiology of breast cancer and call for further research exploring the underlying mechanisms of this association to elucidate whether it is primarily due to di-

rect effects of caloric restriction on breast cell growth and development, to amenorrhea and associated hypoestrogenism, or to a decreased level of growth factors.

Author Contributions: Dr Ekblom had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical expertise; study supervision: Michels, Ekblom.

Acquisition of data: Ekblom.

Drafting of the manuscript; obtained funding: Michels.

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Role of the Sponsor: The US Department of Defense Breast Cancer Research Program had no involvement in, or control over, the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation of the data; or in the preparation, review, or approval of the manuscript.

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Common sense is judgment without reflection which is shared by an entire class, a people, a nation, or the whole human race.

—Giovanni Battista Vico (1668-1744)